(54) Titre : MEMBRANE DE FLUORURE DE POLYVINYLIDENE
(54) Title: POLYVINYLIDENE FLUORIDE MEMBRANE

(57) Abrégé/Abstract:

The present invention provides an isotropic, skinless, porous, polyvinylidene fluoride membrane having a K_{UF} of at least about 15 psi (103 kPa), and preferably below about 50 psi (345 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). The present inventive membrane preferably has a titer reduction of at least about 10^8 against T_1 bacteriophage, more preferably also against PR772 coliphage, and even more preferably also against PP7 bacteriophage. The present inventive membrane can have a thickness of about 20 mil (500 µm) or less and even as low as about 5 mil (125 µm) or less. The present invention also provides a method of preparing such a membrane by providing a casting solution comprising polyvinylidene fluoride and a solvent therefor, heating the casting solution to a uniform temperature of about 57 °C to about 60 °C, spreading the casting solution onto a substrate to form a film, quenching the film in a quench bath so as to form a porous membrane, and washing and drying the porous membrane.

ABSTRACT

The present invention provides an isotropic, skinless, porous, polyvinylidene fluoride membrane having a K_{UF} of at least about 15 psi (103 kPa), and preferably below about 50 psi (345 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). The present inventive membrane preferably has a titer reduction of at least about 10^8 against T_1 bacteriophage, more preferably also against PR772 coliphage, and even more preferably also against PP7 bacteriophage. The present inventive membrane can have a thickness of about 20 mil (500 μm) or less and even as low as about 5 mil (125 μm) or less. The present invention also provides a method of preparing such a membrane by providing a casting solution comprising polyvinylidene fluoride and a solvent therefor, heating the casting solution to a uniform temperature of about 57 °C to about 60 °C, spreading the casting solution onto a substrate to form a film, quenching the film in a quench bath so as to form a porous membrane, and washing and drying the porous membrane.

POLYVINYLIDENE FLUORIDE MEMBRANE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a porous membrane comprising polyvinylidene fluoride, as well as to methods of preparing and using such a membrane. The present inventive membrane has been found to be particularly

5   useful in the filtration of pharmacological and other solutions, particularly in the removal of viruses from such solutions.

BACKGROUND OF THE INVENTION

10   In preparing solutions which are intended for administration to animal or human hosts, such as pharmacological and life-support solutions, it is important that such solutions be as free as possible from substances which may cause adverse reactions in the host.

15   One such contaminant which is of particular concern are viruses. Viruses are the cause of many of the world's dreaded diseases, such as, for example, polio, hepatitis, and AIDS.

Several different physical and nonphysical processes

20   are presently used to either remove or inactivate viruses. Nonphysical processes used to inactivate viruses include, for example, heat pasteurization and chemical treatment. However, these processes do not affect all viruses equally. Moreover, if biotherapeutic

25   agents are present, such agents can also become inactivated. Further, the chemicals used in chemical treatments can have a deleterious effect upon a host.

An alternative approach involves physical separation processing. Such processes use filtration membranes,

e.g., symmetric or asymmetric microporous or ultrafiltration membranes, to remove viruses from a solution. Such membranes remove viruses by either adsorption, sieving, or a combination of adsorption and

5   sieving. Sieving is generally preferred over adsorption because of the greater control that can be exercised over the sieving process and because sieving is less likely to allow a virus to accidentally pass through the filtration membrane.

10   When filtering viruses, one must take into account the size of the targeted viruses in order to select the appropriate filtration medium. While not all viruses are of the same size, viruses are typically characterized as either "large" viruses or "small" viruses. The large

15   viruses include viruses of about 0.08 μm in effective diameter and larger, e.g., adenoviruses, rheoviruses, and herpes viruses. The small viruses include viruses which are about 0.025-0.028 μm in effective diameter, e.g., hepatitis viruses, polio viruses, and parvoviruses.

20   The efficient sieving of viruses is limited at present by available filtration membranes. While both microporous and ultrafiltration membranes have been proposed to sieve viruses, each of these membranes are inadequate in various respects.

25   Microporous membranes are characterized by being isotropic and skinless. In other words, they have a consistent pore structure, and their ability to remove particles, as measured by, for example, titer reduction, is dependent on the pore size and thickness of the

30   membrane. The smallest average pore size currently available in this type of membrane, however, is only about 0.04 μm, e.g., Ultipor N66-NDP (Pall Corporation, Glen Cove, New York). While such membranes are able to remove the relatively large viruses using membranes of

35   reasonable thickness, they cannot generally remove those which fall into the smaller size category. Attempts to

prepare a microporous membrane having smaller pores have been unsuccessful to date.

Ultrafiltration membranes are characterized by being asymmetric, i.e., they possess a nonuniform pore size across their thickness. Specifically, such membranes typically consist of an integral bilayer, wherein one layer is a thin skin which exhibits what has been termed slit-like fissures, while the other layer is a thick substructure containing a high concentration of finger-like intrusions or macrovoids. The thin skin has a relatively small pore size, while the thick substructure has a relatively larger pore size. It is the skin, which is integral with the balance of the membrane, that provides the membrane with its filtration rating. Ultrafiltration membranes are generally available in a pore diameter range of from 0.001 to 0.02 μm.

Ideally, the integral skin completely covers the macrovoids of the thick substrate. In practice, however, the skin above the macrovoids almost always contains significant defects, such as cracks, pinholes, and other defects and imperfections, which either breach the skin layer or lead to failure upon use. Thus, there cannot be certainty regarding the integrity of the membrane and its removal rating.

Thus, although ultrafiltration membranes are used in practice, the membranes are used on a statistical basis in view of the integrity defects. That is, since only a small portion of the liquid being filtered will pass through any defects, and as only a portion of all the liquid being filtered contains the undesirable material sought to be removed, the probability is that only a small amount of such material will pass through the membrane. While this may be acceptable for certain applications, it is unacceptable for many other applications, particularly in those situations in which the filtered liquid is intended to be administered to a human or animal, and any viruses or the like which have

4

passed through the membrane can create a serious health problem for the recipient.

Moreover, the manufacture of acceptable ultrafiltration membranes is difficult in view of their
5   structure and the defects which invariably accompany that structure. To date, no ultrafiltration membrane has been manufactured which is in fact free from defects. Furthermore, because of the extremely thin skin (on the order of· a few microns in thickness) which is responsible
10   for all of the filtration characteristics of a ultrafiltration membrane, it is quite difficult to replicate on a consistent basis ultrafiltration membranes that possess the same level of defects, pore size, and pore size distribution. In addition, the integrity and
15   other properties of such membranes cannot even be readily tested after manufacture and before actual use because typical testing procedures, e.g., "bubble point" and K_L tests, would require such exceedingly high test pressures so as to crush or otherwise damage the membranes.
20   Thus, a serious need remains for a filtration membrane which is capable of providing for the efficient and predictable removal of small particles, such as viruses, from a fluid. Such a membrane should preferably exhibit minimal adsorption properties in order to prevent
25   fouling and other undesirable filtration effects. Further, the filtration membrane should be readily reproducible and integrity testable prior to actual use. A commercially adaptable method for preparing such a membrane would also be desirable. The present invention
30   provides such a filtration membrane, as well as related methods of preparing and using such a membrane. These and other objects and advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention
35   provided herein.

BRIEF SUMMARY OF THE INVENTION

The present invention provides an isotropic, skinless, porous, polyvinylidene fluoride membrane having a K_{UF} of at least about 15 psi (103 kPa), and preferably

5   below about 50 psi (345 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). The present inventive membrane preferably has a titer reduction of at least about 10^8 against T_1 bacteriophage, more preferably also against PR772

10 coliphage, and even more preferably also against PP7 bacteriophage. The present inventive membrane can have a thickness of about 20 mil (500 μm) or less and even as low as about 5 mil (125 μm) or less.

The present invention also provides a method of

15 preparing such a membrane by providing a casting solution comprising polyvinylidene fluoride and a solvent therefor, heating the casting solution to a uniform temperature of about 57 °C to about 60 °C, spreading the casting solution onto a substrate to form a film,

20 quenching the film in a quench bath so as to form a porous membrane, and washing and drying the porous membrane.

BRIEF DESCRIPTION OF THE DRAWINGS

25 Figures 1A and 1B are scanning electron micrographs of a polyvinylidene fluoride membrane of the present invention taken at 500X magnification (Figure 1A) and 5.0KX magnification (Figure 1B).

Figures 2A and 2B are scanning electron micrographs

30 of the top (Figure 2A) and bottom (Figure 2B) of a polyvinylidene fluoride membrane of the present invention taken at 10.1KX magnification.

Figure 3 is a graph depicting a curve showing the relationship between the casting solution temperature

35 (°C) and the resulting membrane K_{UF} (psi and kPa).

Figure 4 is a graph depicting a curve showing the relationship between pressure drop across the membrane

(ΔP) divided by the thickness of the membrane (in. Hg/mil and cm Hg/μm; logarithmic scale) and membrane K_{UF} (psi and kPa).

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The present invention provides a novel isotropic, skinless, porous membrane having a pore rating which is lower than has been previously accomplished with such membranes. The pore size characteristics of the present inventive membrane can be characterized in terms of K_{UF} as well as titer reduction.

Specifically, the present invention provides an isotropic, skinless, porous polyvinylidene fluoride membrane having a K_{UF} of at least about 15 psi (103 kPa), preferably at least about 17 psi (117 kPa), and most preferably at least about 20 psi (138 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). The present inventive membrane will typically have a K_{UF} below about 50 psi (345 kPa), e.g., about 15 psi (103 kPa) to about 50 psi (345 kPa), and will more generally have a K_{UF} below about 40 psi (276 kPa), e.g., about 17 psi (117 kPa) to about 40 psi (276 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). Even more generally, the present inventive membrane will have a K_{UF} below about 30 psi (207 kPa), e.g., about 18 psi (124 kPa) to about 30 psi (207 kPa), when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m).

The present inventive membrane can also be characterized by its titer reduction against various phages. The present inventive membrane preferably has a titer reduction of at least about 10^8 against T_1 bacteriophage, more preferably also against the smaller PR772 coliphage, and most preferably against the even smaller PP7 bacteriophage as well. The titer reduction of a particular membrane of the present invention is

quite predictable based on the K_{UF} and thickness of the membrane. Moreover, the titer reduction can be tailored to be within rather strict confines, evidencing a narrow pore size distribution. For example, the present

5   inventive membrane can have a titer reduction of at least about 10^8 against T_1 bacteriophage, or even against PR772 coliphage, while having a titer reduction of about 10^2 or less against PP7.

The present inventive membrane can be prepared so as

10   to be of any suitable thickness and can be layered so as to achieve a desired thickness. Generally, the present inventive membrane will have a thickness of about 20 mil (500 μm) or less, preferably about 10 mil (250 μm) or less, and most preferably about 5 mil (125 μm) or less.

15   For most applications, the present inventive membrane can have a thickness of about 3 mil (75 μm) to about 5 mil (125 μm). The present inventive membrane can be of these various thicknesses and still be characterized by the aforesaid K_{UF} and/or titer reduction values. Thus, while

20   the membrane of the present invention can be prepared so as to be quite thin, e.g., about 1-5 mil (25-125 μm) in thickness or even as thin as 1-3 mil (25-75 μm) in thickness, the present inventive membrane can still provide excellent titer reduction against viruses.

25   Since the present inventive membrane is isotropic, it has a substantially uniform and symmetrical pore structure. Representative membranes of the present invention are shown in the scanning electron micrographs of Figures 1A (500X) and 1B (5.00KX), which depict the

30   fine and uniform pore structure of the membrane, and in the scanning electron micrographs of Figures 2A and 2B (both 10.1KX), which depict the top and bottom views of the same membrane. In addition, the isotropic nature of the present inventive medium is illustrated by the

35   straight line plot in the graph of Figure 4. That figure depicts a plot of membrane pressure drop (ΔP) independent of membrane thickness (in. Hg/mil and cm Hg/mil) on a

logarithmic scale versus the membrane K_{UF} (psi and kPa). The resulting straight line curve is indicative of an isotropic membrane.

5   $\underline{K_{UF}\ Determination}$

Test methods known as the "bubble point" (ASTM F316-86) and the K_L (U.S. Patent 4,340,479) test methods have been employed in the past to evaluate the pore size characteristics of microporous membranes. Although these
10 test methods, particularly the K_L test method, can be used to evaluate the present inventive membrane, such tests require high pressures in conjunction with membranes of very small pores, which can cause reliability problems. Thus, the present inventive membrane is preferably
15 characterized by use of the K_{UF} test method which was developed by Pall Corporation to provide a means to more reliably evaluate the pore size and membrane integrity of membranes with very small pore ratings.

The K_{UF} test method is described in U.S. patent No.
20 5,480,554. In accordance with the K_{UF} test method, the membrane to be tested is first thoroughly wetted with a wetting liquid that is capable of fully wetting the membrane. A displacing liquid, which is immiscible with the wetting liquid used to wet the membrane but has a
25 low, stable interfacial tension, is placed in contact with the upstream side of the wetted membrane. Pressure is then incrementally applied to the displacing liquid, and the flow of the displacing liquid through the membrane is measured as a function of the applied
30 pressure. The displacing liquid should be stable but not miscible with the wetting liquid, and the interfacial tension between the two liquids should be about 10 dynes/cm (10 mN/m) or less. Controlling the interfacial tension to less than 10 dynes/cm (10 mN/m) allows fluid
35 displacement to be achieved at much lower pressures than in similar testing

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normally performed with a water/air interface (i.e., in the K_L or bubble point test methods). In addition, it is important that the interfacial tension between the two liquids remain constant during the test procedure. A

5 plot of the flow rate of displacing liquid, per unit area of the membrane, through the membrane as a function of applied pressure can be made, and a straight line can be drawn through the steep part of the resulting curve, using regression analysis, which will intersect the

10 horizontal axis at a given pressure value. This point of intersection is deemed the K_{UF} value and is directly related to the pore size of the membrane. Since there is no diffusive flow through a membrane which is free of defects, the flow rate of the displacing liquid through

15 the membrane prior to the K_{UF} value is zero, i.e., a flat line in the typical plot of flow rate versus pressure.

   The K_{UF} values recited herein were determined using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m). In particular, the K_{UF} values recited

20 herein were determined using n-pentanol, saturated with water, as the wetting liquid, and water, saturated with n-pentanol, as the displacing liquid. The immiscible phases are mutually saturated to ensure that the interfacial tension between the liquids, which is about

25 4.4 dynes/cm (4.4 mN/m) at ambient temperature, does not change due to dissolution of one phase into the other. Other factors such as temperature should also remain relatively constant during the test procedure so as to avoid significant changes in the interfacial tension

30 between the immiscible liquids during the test. While other liquid pairs can be used to determine K_{UF}, such as, for example, n-butanol and water, n-pentanol and water were used herein because the thus obtained K_{UF} values were in a convenient range for measurement and because the

35 high mutual solubilities of n-pentanol and water ensured that if there were selective adsorption of one of the components by the membrane, then such adsorption would

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have little or no effect on the obtained K_{UF} value. Other alcohol/water systems include, for example, n-octanol/water and n-hexanol/water, and other nonalcohol-based liquid pairs, could, of course, be similarly utilized in determining K_{UF}.

The interfacial tensions for several organic liquids that form a phase boundary with water as reported in the book Interfacial Phenomena, 2nd ed., by J. T. Davies and E. K. Rideal (1963), are set forth below, along with the solubilities of the various compounds in water as reported in the Chemical Rubber Handbook (CRC), 1970 ed.

Compound	Interfacial Surface Tension (dynes/cm or mN/m)	Temp. (°C)	Solubility (g/100 g H_2O)
ethyl ether	10.7	20	7.5
n-octanol	8.5	20	0.054
n-hexanol	6.8	25	
		20	0.6
aniline	5.85	20	
n-pentanol	4.4	25	
		22	2.7
ethyl acetate	2.9	30	
		15	8.5
isobutanol	2.1	20	
		15	10.0
n-butanol	1.8	25	
	1.6	20	
		15	9.0

Although only organic liquids and water are set forth in the table immediately above, the K_{UF} test method,

as previously indicated, can be performed using any pair of immiscible liquids.

In accordance with the K_{UF} test method, the wetting liquid may be a single liquid compound, such as n-

5   octanol, and the displacing liquid also may be a single compound, such as water, which is substantially insoluble in the n-octanol. Alternatively, the wetting liquid may be an equilibrium mixture comprising a first liquid compound, such as n-pentanol, that is saturated with a

10   second liquid compound, such as water. The second liquid compound, saturated with the first, is then used as the displacing liquid. With respect to either embodiment, it is important that the interfacial tension between the two liquids remains relatively constant while performing the

15   test. It is thus recommended that the phases be compositionally stable, i.e., when the phases are in contact no net flux of either fluid occurs across the interface. Thus, there is no substantial variation in the solubility of the displacing liquid in the wetting

20   liquid, which, if present, could affect the results.

In practice the K_{UF} test is usually run with each of the immiscible phases saturated with the fluid in which it is in intimate contact. For example, the solubility of n-pentanol in water is 2.7 g per 100 g of water at 22

25   °C. Since some n-pentanol will dissolve in water it is preferred that the water phase be saturated with n-pentanol. Likewise, with the n-pentanol phase, it is preferred that it be saturated with water. Mutually saturated phases are easily achieved by shaking a mixture

30   containing sufficient quantities of each of the fluids together in a container or separatory funnel. In the tests and examples described herein, the organic phase was in each case used to wet the membrane. It is an obvious extension of the method to reverse the fluids,

35   i.e., wetting the membrane with the aqueous phase and pressurizing the upstream side of the membrane with the organic phase.

The absolute K_{UF} values, of course, will vary
depending on the particular alcohol/water system,
although the values obtained using other alcohol/water
systems can be generally correlated to the n-
5   pentanol/water system K_{UF} values through use of the ratio
of their respective interfacial tensions. For example, a
K_{UF} value of about 45 psi (310 kPa) in the n-
pentanol/water system is equivalent to a K_{UF} value of
about 18 psi (124 kPa) in the n-butanol/water system
10   (i.e., 45 psi (or 310 kPa) x 1.8/4.4).

Titer Reduction

Titer reduction has reference to the ability of a
particular membrane to remove a given particle from a
15   fluid. As such, titer reduction is a standard measure of
a membrane's ability to remove biological organisms, such
as bacteria and viruses. While any suitable particle may
be used in determining titer reduction, the titer
reduction of the present inventive membrane was evaluated
20   by challenging the membrane with T_1 and PP7
bacteriophages (generally a 50:50 mixture of the two
bacteriophages at a level of 10^9-10^{10} bacteriophages/ml)
in a gel phosphate buffer. For purposes of the
evaluations reported herein, E. coli ATCC # 11303 was the
25   source of the T_1 phage, and P. aeruginosa ATCC # 15612
was the source of the PP7 phage. In addition to the T_1
and PP7 bacteriophages, the present inventive membrane
was also tested against the PR772 coliphage. The source
of the PR772 phage for purposes of the evaluations
30   reported herein was Prof. H.W. Ackerman, Department of
Microbiology, Faculty of Medicine, Laval University,
Quebec, Canada.

The titer reduction of a membrane is defined as the
ratio of the phage contained in the influent to that
35   obtained in the effluent. As the size of the T_1 phage is
about 0.078 μm, the size of the PR772 phage is about
0.053 μm, and the size of the PP7 phage is about 0.027

μm, these phages provide excellent models for assessing the removal efficiency of a membrane with regard to larger, intermediate-sized, and smaller viruses. A membrane is generally considered to have an "absolute"

5   removal ability with respect to a particular particle, e.g., the T_1 phage as representative of larger viruses, when it has at least a 10^8, and preferably at least a 10^{10}, titer reduction against that particle. Of course, an absolute removal ability of a membrane with respect to

10   the PR772 or PP7 phages would confirm the absolute removal ability of that membrane with respect to larger viruses.

       Since these biological organisms are capable of rapid replication, they allow for easy detection of the

15   most minute quantities in the filtrate of a test solution. Thus, the inability to detect any quantity of a particular such model biological organism in the filtrate of a test solution is excellent confirmation of the fact that the particular membrane actually prevented

20   all of the biological organism in the challenge liquid from passing through the membrane. Moreover, since the quantity of viruses found as contaminants in most commercial processes rarely exceeds about 10^4/ml, the ability of the present inventive membrane to have a titer

25   reduction of 10^8 or higher can provide nearly absolute assurance of the removal of all viruses from a wide variety of liquids, particularly those involved in commercial processing, e.g., pharmaceutical production.

       Titer reduction is a function of the K_{UF} value of a

30   membrane and the thickness of the membrane. Since the pressure drop across a membrane is exponentially affected by the K_{UF} of a membrane, while the pressure drop across a membrane is only linearly affected by the thickness of the membrane, small improvements in the titer reduction

35   of a particular membrane can generally be accomplished in a more economical manner by increasing the thickness of

the membrane, e.g., by providing multiple layers of the same membrane.

Pressure Drop

5   The pressure drop across a membrane is quite important in the use of such membranes for filtration purposes. The present inventive membrane advantageously provides the desired titer reduction against a certain particulate with a satisfactory pressure drop (ΔP) across

10   the membrane. The pressure drops referenced herein were calculated using conventional techniques, such as described in U.S. Patent 4,340,479, and all pressure drop values reported herein (in. Hg (cm Hg) or psi (kPa)) were determined at a constant air flow rate of 2 ft/min (61

15   cm/min).

Preparation Method

        The membranes of the present invention are prepared from polyvinylidene fluoride (PVDF) using the wet casting

20   procedure described in U.S. Patent 4,340,479 in conjunction with the particular temperature constraints discussed herein. Any suitable polyvinylidene fluoride may be used, such as Kynar® 761 and 761 PVDF resins. The polyvinylidene fluoride will typically have a molecular

25   weight of at least about 5,000 daltons, preferably a molecular weight of at least about 10,000 daltons.

        The present inventive method of preparing the membranes described herein comprises providing a casting solution comprising polyvinylidene fluoride and a solvent

30   therefor, heating the casting solution to a uniform temperature of about 57 °C to about 60 °C, spreading the casting solution onto a substrate to form a film, quenching the film in a quench bath so as to form a porous membrane, and washing and drying the porous

35   membrane. The temperature of the casting solution is directly related to the K_{UF} of the resulting membrane, as is illustrated in the graph of Figure 3 which contains a

plotted curve of casting solution temperature (°C) versus resulting membrane K_{UF} (psi and kPa). For example, a casting solution temperature of about 58 °C will result in the formation of a membrane having a K_{UF} of about 31

5   psi (214 kPa), while a casting solution temperature of about 60 °C will result in the formation of a membrane having a K_{UF} of about 17 psi (117 kPa).

It has been surprisingly discovered that the temperature at which the polyvinylidene fluoride casting

10   solution is maintained is quite critical to the preparation of the present inventive membrane. Great care must be exercised to ensure that the casting solution temperature is uniform, i.e., at a particular temperature ± 0.01 °C, so as to ensure the substantial

15   uniformity of the pore structure within the membrane. Moreover, while not intending to be bound to any particular theory underlying the present invention, it appears that the casting solution has at least a short-term memory, such that it is difficult to prepare the

20   present inventive membrane of a desired K_{UF} value if the temperature of the casting solution has significantly exceeded about 60 °C at any time during the processing of that casting solution, even if the temperature is subsequently lowered to below about 60 °C. One possible

25   explanation for this apparent effect is that, while a single temperature may be reported for the casting solution, the reported temperature is actually an average of a range (or distribution) of temperatures within the casting solution such that a significant portion of the

30   casting solution may actually be well above the reported temperature. This may explain the particular success in preparing suitable membranes through use of the preferred techniques of the present inventive method, which involve approaching the desired temperature of the casting

35   solution with increasingly higher precision heating devices (which not only efficiently provides a uniform temperature for the casting solution but also

significantly reduces the possibility that some portion
of the casting solution will significantly exceed about
60 °C, and more preferably the desired final temperature
of the casting solution, at any given step of the heating
5   process).

While the present inventive method can be carried
out in a variety of suitable manners, a preferred
embodiment of the present inventive method begins with
the formation of a solution consisting of polyvinylidene
10   fluoride in powder form, a solvent for the resin,
advantageously dimethylacetamide, and a nonsolvent,
advantageously isopropanol. The solution comprises about
10 to about 20 wt.%, and advantageously from about 15 to
17 wt.%, polyvinylidene fluoride. The balance of the
15   solution comprises the solvent and nonsolvent in a weight
ratio ranging from about 90:10 to about 70:30, preferably
about 80:20.

The temperature of the polymer solution is then
raised to the desired casting solution temperature.
20   Small quantities of polymer can be efficiently handled at
uniform temperatures in a one-step process, e.g., a few
hundred grams of polymer in a one liter solution can be
uniformly heated in a jacketed kettle with impeller
stirring at high rpm. With larger quantities,
25   particularly commercial production quantities, it is not
practical to use a one-step heating process such as a
jacketed kettle due to the significant temperature
variations in the casting solution which must be avoided
to satisfactorily prepare the present inventive membrane.
30   As regards larger quantities, therefore, the
temperature of the casting solution is preferably raised
in stages so as to carefully control temperature
uniformity while minimizing the time required to raise
the temperature. At each successive stage, the
35   temperature is raised and brought closer to the casting
temperature necessary to prepare a membrane of the
desired K_{UF}, but in a manner which ensures greater

isopropanol, and washed, e.g., with deionized water, by conventional techniques so as to form the present inventive membrane.

   After washing is completed, the wet membrane is
5 collected and dried. While drying may be undertaken by any suitable means, e.g., by heat in an oven, it has been discovered that drying by the direct application of heat, as in an oven, results in an undesirable increase in pore size of the resulting membrane. This has been overcome,
10 however, by the application of microwave energy to the membrane in order to effect the drying of the membrane. Microwaves having a frequency of about 24 MHz are preferably used, although any frequency can be used so long as the pore size or K_{UF} value of the membrane is not
15 unduly effected.

Heat-Treatment

   The resulting polyvinylidene fluoride membrane can be heat-treated or annealed, if desired, to improve its
20 properties. In particular, the present inventive membrane can be heated under conditions to improve the strength and subsequent hydrophilization of the membrane.

   Preferably, the present inventive membrane is heated to a temperature of at least about 80 °C for a time
25 sufficient to achieve a state such that, when subsequently hydrophilized, the resultant hydrophilized membrane has substantially uniform hydrophilic properties. Of course, the present inventive membrane should not be heated at so high a temperature that the
30 membrane becomes soft and deforms, either under its own weight or due to tension from any mechanical means by which the membrane is supported during the heating process. Typically, the upper temperature limit will be about 160 °C. The amount of time of heating will vary
35 with the heating temperature and nature of the membrane being heated. For example, small pieces of membrane in flat sheet form which are in direct contact with a high

temperature surface may require only a brief exposure, e.g., less than one minute, to heat, while a rolled membrane of several hundred linear feet may require many hours of heating at low temperature for the membrane to

5 reach a suitable equilibrium temperature. Most preferably, the present inventive membrane is heated to a temperature of about 120 °C for about 24-72 hours, especially for about 48 hours.

The heat-treatment of the present inventive membrane

10 can be effected without the membrane being restrained; however, the membrane preferably is dimensionally restrained during the heat-treatment so as to minimize or avoid dimensional changes in the membrane, e.g., shrinkage. Any suitable means can be used to

15 dimensionally restrain the membrane. For example, the membrane can be placed into a frame or can be wound onto a core or roll, preferably with an interleaved material, such as a fibrous nonwoven material, to prevent layer-to-layer contact of the membrane. Most preferably, the

20 present inventive membrane is heat-treated in roll form interleaved with a polyester fibrous nonwoven material.

The heat-treatment of polyvinylidene fluoride membranes is more fully described in U.S. Patents 5,196,508 and 5,198,505. Those patents also describe the

25 improvements in surface modifications which can be obtained by heat-treating polyvinylidene fluoride membranes.

Surface Modification

30 The resulting polyvinylidene fluoride membrane is hydrophobic and exhibits a significant tendency to adsorb proteins and the like, which may be present in the liquid being filtered. These characteristics are undesirable inasmuch as they contribute to a higher pressure drop

35 across the membrane and can ultimately result in the premature fouling of the membrane and/or, in certain cases, the formation of a secondary sieving layer on the

uniformity (i.e., a narrower temperature distribution) so as to ensure that the casting solution does not exceed the desired casting temperature.

5   In particular, a larger quantity of polyvinylidene fluoride can be placed into a thermostatically controlled tank and dispersed in a suitable mixture of solvent and nonsolvent. During the mixing of the casting solution, the temperature of the tank is maintained at a temperature which allows the contents therein to reach a

10   temperature of about 47 °C to about 51 °C, which is well below the desired casting solution temperature. This average temperature is selected so as to ensure that no significant portion of the solution exceeds the desired casting solution temperature between about 57 °C and

15   about 60 °C. The components should remain in the tank until the polyvinylidene fluoride has dissolved, and the resulting solution is uniformly heated with that equipment, e.g., for about 16 hours or so.

       The casting solution is then preferably transported

20   through a heat exchanger to raise its temperature to about 52 °C and then passed through an in-line mixer (or other suitable high precision heating device) which raises the temperature of the casting solution to the desired uniform casting solution between about 57 °C and

25   about 60 °C ± 0.01 °C. The uniformity of temperature is quite important to the uniformity of the pore structure within the resulting membrane.

       After the casting solution is heated in the in-line mixer, and before the casting solution is spread (i.e.,

30   cast) onto a substrate, the viscosity of the casting solution will typically be increased by passing the casting solution through a viscosity leveler, e.g., another heat exchanger which lowers the temperature of the casting solution to about 35 °C or so. The casting

35   solution is then spread onto a suitable substrate, e.g., mylar, quenched by exposure to a suitable quench bath, e.g, an aqueous solution of dimethylacetamide and

surface of the membrane. As a result, the present inventive membrane is preferably surface modified to render it hydrophilic (i.e., having a critical wetting surface tension (CWST) of at least about 72 dynes/cm (72 mN/m) as determined by the CWST test disclosed in U.S. Patent 4,880,548) and less susceptible to protein adsorption and fouling.

Such surface modification of the present inventive membrane can be carried out in any suitable manner and is preferably accomplished by graft polymerizing a suitable monomer onto the surface of the membrane. Preferred examples of such monomers include acrylic or methacrylic monomers having alcohol functional groups, such as, for example, hydroxyethylacrylate, hydroxyethylmethacrylate, hydroxypropylacrylate, hydroxypropylmethacrylate, and combinations thereof, particularly hydroxypropylacrylate and/or hydroxyethylmethacrylate. These monomers can be combined with small amounts of acrylic monomers having no alcohol functional groups, such as methyl methacrylate, as described in U.S. Patent 5,019,260.

Any suitable means may be used to polymerize the suitable monomers onto the membranes of the present invention. Radiation grafting is the preferred technique to achieve such a result. The source of radiation can be from radioactive isotopes like Cobalt 60, Strontium 90, and Cesium 137, or from machines like x-ray machines, electron accelerators, and ultraviolet equipment. Preferably, however, the radiation is in the form of electron beam radiation. It has been found that, by using this form of radiation, a very uniform distribution of radiation can be provided. This in turn results in a final product which is grafted more uniformly as compared to those membranes which are grafted using other radiation sources, e.g., Cobalt 60.

Grafting will typically be achieved by either irradiating the membrane and then exposing it to a suitable solution of the monomer or irradiating the

membrane while it is exposed to a suitable solution of
the monomer. Regardless of which procedure is used, the
grafting should be conducted in the absence of oxygen,
e.g., under a nitrogen atmosphere, since oxygen will
5 react with the reactive sites created by radiation
exposure, thereby lowering the number of sites available
for the desired polymer bonding. If the membrane is
irradiated prior to immersion in the monomer solution,
the membrane should contact the monomer solution as
10 quickly as possible to avoid undesirable reactions
resulting in the loss of reactive sites for bonding the
polymer to the surface of the membrane. The monomer
solution can comprise any suitable concentration of the
monomer to be graft polymerized, typically 1-10 vol.%
15 monomer in a solvent system, generally water by itself or
with a suitable alcohol such as t-butyl alcohol. The
preferred monomer solution in the context of the present
invention is 4 vol.% hydroxypropylacrylate, 25 vol.% t-
butyl alcohol, and 71 vol.% deionized water. The details
20 and parameters of the polymer grafting of membranes is
well known in the art.

While the graft polymerization can be carried out in
the absence of crosslinking agents, it is preferred that
such crosslinking agents be used, particularly when the
25 aforementioned acrylate monomers are graft polymerized
onto the surface of the membrane. Any suitable
crosslinking agent can be used in the context of the
present invention. Suitable crosslinking agents include
di- or poly-acrylates and methacrylates of diols and
30 polyols, particularly linear or branched aliphatic diols
such as ethylene glycol, 1,2-propylene glycol, diethylene
glycol, dipropylene glycol, dipentylene glycol,
polyethylene glycol, polypropylene glycol,
polytetramethylene-oxide glycol, and poly(ethylene
35 oxide-copropylene-oxide)glycol, as well as triol
acrylates such as trimethylolpropane triacrylate.
Examples of other crosslinking monomers that may be used

in the instant invention include allyls, maleimides, unsaturated dicarboxylic acids, aromatic vinyl compounds, polybutadienes, and trimellitic acid esters. Other suitable crosslinking agents are described in U.S.

5   Patents 4,440,896, 4,753,988, 4,788,055, and 4,801,766.

Polyethylene glycol dimethacrylates wherein the molecular weight of the polyethylene glycol is about 200 to about 600, are preferred crosslinking agents in the context of the present invention. Polyethylene glycol

10 600 dimethacrylate, especially in conjunction with radiation grafting hydroxypropylacrylate onto the surface of the membrane, is the most preferred crosslinking agent.

The crosslinking agent can be utilized in any

15 suitable amount. Typically, the crosslinking agent will be added to the grafting solution in an amount of about 0.025 vol.% to about 5 vol.%, more typically in an amount of about 0.05 vol.% to about 2 vol.%. Thus, for example, a monomer solution containing 4 vol.%

20 hydroxypropylacrylate in water and t-butyl alcohol preferably contains about 0.5 vol.% polyethylene glycol 600 dimethacrylate as the crosslinking agent.

Illustrative Uses

25 The present inventive membrane can be used in any suitable application, including many applications in which ultrafiltration membranes are currently being used. In view of the excellent titer reduction of the membrane against viruses and similar sized particulates, the

30 present inventive membrane has particular utility in the filtration of pharmacological liquids and the like, although the present inventive membrane can be used to filter any suitable fluid.

Accordingly, the present invention provides a method

35 of filtering a fluid comprising passing a fluid through the present inventive membrane, particularly an isotropic, skinless, porous, polyvinylidene fluoride

membrane having a K_{UF} of at least about 15 psi (103 kPa) when tested using liquid pairs having an interfacial tension of about 4 dynes/cm (4 mN/m) and/or having a titer reduction of at least about 10^8 against T_1

5   bacteriophage. The fluid to be passed through the present inventive membrane can comprise viruses, e.g., in excess of 10^2/ml or even 10^4/ml, before being passed through the membrane, which viruses can be removed from the fluid such that the fluid comprises less than 10^2/ml

10   or even no viruses after being passed through the membrane. Thus, the present inventive membrane can be used to treat fluids to reduce or remove viruses therein and also can be used to recover and concentrate viruses from fluids for viral identification, testing, and the

15   like.

The ability of the present inventive membrane to be integrity tested with relative ease, and to be consistently prepared on a commercial basis, enables the present inventive membrane to provide a predictable

20   removal rating for given substances. Moreover, the excellent removal characteristics of the present inventive membrane are obtained at a reasonable pressure drop across the membrane. Thus, to the extent that the present inventive membrane can be used in applications in

25   which ultrafiltration membranes are currently being utilized, the present inventive membrane will prove much more desirable than, and will outperform, ultrafiltration membranes in those same applications.

The present inventive membrane can be used alone or

30   can be mated with a suitable support structure. Similarly, the present inventive membrane can be used in suitable filters, filtration cartridges, and the like. Of course, in view of the highly uniform nature of the pore structure within the present inventive membrane, as

35   well the low susceptibility to protein adsorption of the grafted embodiment of the membrane, the present inventive membrane can be used in dead-end filtration applications,

as well as in tangential or cross-flow filtration
applications.

The present inventive membrane in expected to be
especially useful in filter elements, such as filter
5   cartridges, which are generally described in U.S. Patent
4,340,479. Preferred filter elements utilizing the
present inventive membrane comprise the present inventive
membrane in sheet form, wherein the sides of the membrane
have been overlapped and sealed to form a tubular
10 configuration having an exterior surface, an interior,
and two ends, and end caps sealed to the ends of the
tube, wherein at least one of the end caps has a central
aperture providing access to the interior of the tube,
and all of the seals are fluid-tight. The present
15 inventive membrane is preferably corrugated in such a
filter element so as to provide a large membrane surface
area for the volume of the filter element. At least one
of the sides of the membrane will typically be adhered to
a porous support layer, and, in such a situation, the
20 membrane and porous support layer will generally both be
corrugated. The filter element can comprise a single
membrane of the present invention or, more preferably,
comprises multiple such membranes adhered together. When
there are multiple membranes in the filter element, the
25 membranes are preferably separated by a porous support
layer to which each membrane is adhered. The other
aspects of the filter element may be of any suitable
construction and prepared from any suitable material.
For example, the end caps can be prepared from a suitable
30 polymeric material, such as polyester, particularly,
polybutylene glycol terephthalate or polyethylene glycol
terephthalate. The filter element can be constructed
using techniques which are well-known in the art.

35   The following examples further illustrate the
present invention and, of course, should not be construed
as in any way limiting its scope.

<u>Example 1</u>

This example illustrates the preparation of several filtration membranes in accordance with the present invention. The various filtration membranes were prepared using different casting solution temperatures to demonstrate the effect of the casting solution temperature on the K_{UF} of the resulting filtration membrane.

A casting solution was prepared from 17.0 wt.% polyvinylidene fluoride resin, 66.4 wt.% dimethyl acetamide (solvent), and 16.6 wt.% isopropanol (non-solvent). The casting solution was stirred in an enclosed vessel to dissolve the polyvinylidene fluoride resin in the 80:20 w/w solvent/nonsolvent mixture, and the temperature of the casting solution was raised to 50.9 °C and held at that temperature.

Four casting solution samples were then passed through an in-line mixer, and each of the casting solution samples was raised to a different temperature. Each of the solutions was then cooled to increase viscosity, cast as a film onto a substrate, and subjected to a quench bath comprising 42 wt.% water, 51 wt.% dimethyl acetamide, and 7 wt.% isopropanol. The quench bath was maintained at 30 °C. The cast film generally remained in contact with the quench bath for less than one minute. The resulting membrane was then washed with water to remove solvent, and the membrane was microwave dried under restraint to prevent shrinkage. Membranes were thus prepared with each of the four casting solution samples.

The temperatures of each of the casting solution samples and the K_{UF} values of each of the resulting membranes are set forth below.

26

Sample	Temperature ($^\circ$C ± 0.01 $^\circ$C)	K_{UF} (psi) [kPa]
1A	58.22	30 [207]
1B	58.97	23 [159]
1C	59.77	18 [124]
1D	60.17	17 [117]

The resulting data is plotted in the form of casting solution temperature ($^\circ$C) versus K_{UF} (psi and kPa) as the graph of Figure 3. As is apparent from the data, an

10 increase in the casting solution temperature within the range of about 57 $^\circ$C to about 60 $^\circ$C results in a corresponding decrease in the K_{UF} of the filtration membrane prepared from the casting solution.

15 Example 2

This example illustrates the preparation of polyvinylidene fluoride membranes of the present invention which have been provided with a graft-polymerized coating so as to render the membrane

20 hydrophilic and less susceptible to protein binding. The properties of such membranes both before and after grafting were evaluated to demonstrate that the grafting process does not adversely affect the pore rating of the membrane and contributes to only a modest increase in

25 pressure drop across the filtration membrane.

Several membranes of differing K_{UF} values were prepared in accordance with the procedure described in Example 1. A portion of each membrane was grafted using an electron-beam grafting procedure. In particular, the

30 membranes were passed under an electron-beam generator (with 175 kV and 3 mAmp settings) at a rate of 20 ft/min so as to achieve a total radiation dose of 2.4 Mrad. The membranes were then passed into a grafting solution of 4 vol.% hydroxypropylacrylate, 25 vol.% t-butyl alcohol,

and 71 vol.% deionized water, rolled up under a nitrogen atmosphere (i.e., protected from oxygen), and stored for several hours prior to washing free of ungrafted monomer. The grafted membranes were frame-dried at 100 °C for 10

5   min.

The K_{UF}, thickness, and pressure drop (ΔP) across each membrane, in ungrafted and grafted form, were determined, and the results are set forth below.

Sample	Ungrafted Membrane			Grafted Membrane		
	Thickness (mil ± 0.2 mil) [μm ± 5 μm]	K_{UF} (psi) [kPa]	ΔP (in. Hg) [cm Hg]	K_{UF} (psi) [kPa]	ΔP (in. Hg) [cm Hg]	water wettable
2A	1.6 [41]	17 [117]	5.5 [14.0]	18 [124]	5.7 [14.5]	yes
2B	1.6 [41]	24 [165]	10.2 [25.9]	25 [172]	13.8 [35.1]	yes
2C	1.9 [48]	21 [145]	16.7 [42.4]	24 [165]	28.7 [72.9]	yes
2D	2.0 [51]	24 [165]	16.6 [42.2]	25 [172]	28.7 [72.9]	yes
2E	1.9 [48]	17 [117]	8.0 [20.3]	16 [110]	6.8 [17.3]	yes

As is apparent from the resulting data, the grafting of the present inventive membranes renders those membranes desirably hydrophilic, i.e., water wettable,

20   while adversely affecting the K_{UF} and pressure drop characteristics of the membrane in only a modest manner.

Example 3
This example illustrates the excellent titer

25   reductions against various viruses which are characteristic of the present inventive membrane.

Various membranes (142 mm discs of about 1.5-2.0 mil (38-50 μm) thickness) were prepared in accordance with the procedure disclosed in Example 1 and were grafted in

accordance with the procedure disclosed in Example 2.
The grafted membranes were challenged with a 50:50
mixture of T_1 and PP7 bacteriophages (at a level of about
10^{10} bacteriophages/ml) in a gel phosphate buffer. As
5   previously discussed, the size of the T_1 phage is about
0.078 μm, while the size of the PP7 phage is about 0.027
μm. Thus, these bacteriophages are quite representative
of larger and smaller viruses, respectively. The titer
reductions of each membrane, alone or multiple-layered,
10   was determined as the ratio of the particular phage
contained in the influent to that present in the
effluent. The K_{UF} of the ungrafted membrane, the number
of membrane layers tested, and the titer reduction (T_R)
for each phage are set forth below.

Sample	K_{UF} (psi) [kPa]	Number of Layers	T_R (T_1 phage)	T_R (PP7 phage)
3A	23 [159]	3	>1.3×10^{10}	>4.4×10^9
3B	21 [145]	3	>1.3×10^{10}	8.0×10^6
3C	24 [165]	1	>9.1×10^9	5.0×10^1
3D	24 [165]	2	>9.1×10^9	4.0×10^2
3E	24 [165]	3	>1.0×10^9	5.0×10^4
3F	24 [165]	3	>1.0×10^{10}	1.0×10^5
3G	23 [159]	3	>1.0×10^{10}	9.0×10^5
3H	17 [117]	3	>1.0×10^{10}	5.7

25   The resulting data demonstrates that the filtration
membrane of the present invention can have a very high
titer reduction and can be capable of the "absolute"
removal of viruses, as is particularly apparent with
sample 3A. Moreover, this high titer reduction
30   capability can be accomplished with remarkably thin
membranes, as exemplified by sample 3C. In addition, the
resulting data demonstrates that the filtration membrane
of the present invention has a very uniform pore

structure. For example, sample 3H, is capable of removing all of the T_1 bacteriophage while allowing essentially all of the PP7 bacteriophage to pass through. Thus, the sample 3H membrane has a pore size between

5 about 0.078 μm and about 0.027 μm, which is quite a narrow pore size distribution.

Example 4

This example further illustrates the excellent virus

10 titer reduction which is characteristic of the present inventive membrane.

The grafted filtration membrane of Example 3 which was designated sample 3F was challenged with a mixture of PR772 coliphage (at a level of 5.2×10^8 phages/ml) and PP7

15 bacteriophage (at a level of 1.7×10^9 phages/ml) in a gel phosphate buffer. As previously described, the size of the PR772 phage is about 0.053 μm, while the size of the PP7 phage is about 0.027 μm. Thus, these phages are quite representative of intermediate-sized and smaller

20 viruses, respectively. The titer reductions of each membrane, alone or multiple-layered, was determined as the ratio of the particular phage contained in the influent to that present in the effluent. The K_{UF} of the ungrafted membrane, the number of membrane layers tested,

25 and the titer reduction (T_R) for each phage are set forth below.

Sample	K_{UF} (psi) [kPa]	Number of Layers	T_R (PR772 phage)	T_R (PP7 phage)
3G	23 [159]	3	$>5.2 \times 10^8$	2.2×10^6

30 The determined results confirm the excellent titer reduction of the present inventive membrane against intermediate-sized viruses. Moreover, in view of the moderate removal effectiveness of this particular membrane sample against the much smaller PP7 phage, the

35 pore size of this particular membrane sample is shown to

be quite small, i.e., below about 0.053 μm, while the pore size distribution of the sample is also shown to be quite narrow, i.e., from somewhat below about 0.027 μm to below about 0.053 μm.

Example 5

This example illustrates the approximate lower operating limit in terms of pore size of the present inventive membrane as regards a satisfactory titer reduction against larger viruses.

A membrane of 1.8 mil (46 μm) thickness was prepared in accordance with the procedure described in Example 1 and evaluated as regards K_{UF}, pressure drop (ΔP), and titer reduction (T_R) against T_1 and PP7 bacteriophages as described in Example 3. The resulting data is set forth below.

Sample	K_{UF} (psi) [kPa]	ΔP (in. Hg) [cm Hg]	Number of Layers	T_R (T_1 phage)	T_R (PP7 phage)
5A	17 [117]	6.8 [17.3]	1	7×10^6	<10
5B	17 [117]	6.8 [17.3]	2	$>9 \times 10^8$	<10

The resulting data demonstrate that the present inventive membrane having a K_{UF} value of about 17 psi (117 kPa) and a thickness of at least about 3.6 mil (92 μm) will exhibit a titer reduction of over 10^8 against larger viruses. The fact that the present inventive membrane of this example had an "absolute" removal ability with respect to the larger T_1 phage while having essentially no removal ability with respect to the smaller PP7 phage demonstrates that the present inventive medium not only has a pore size of between about 0.078 μm and about 0.027 μm, but that the pore size distribution is quite narrow, i.e., below about 0.078 μm to above about 0.027 μm.

Example 6

This example illustrates the low protein adsorption characteristics of the grafted filtration membrane of the present invention.

5   An immersion load binding test was performed on samples of grafted filtration membranes prepared in accordance with the procedure of Example 2 (samples 6A-6D), as well as on ungrafted controls (samples 6E and 6F). Each membrane was immersed in IgG solution
10   containing ^{125}I goat IgG and 200 μg/ml unlabeled goat IgG for 60 minutes. Each membrane was washed with phosphate buffered saline (PBS) and evaluated for adsorbed IgG. The membranes were then washed with an aqueous solution of 1% SDS in 2 M urea and evaluated again for adsorbed
15   IgG. The results of these evaluations are set forth below.

Sample	Substrate	Grafting Solution	Thickness (mil) [μm]	Post-PBS Adsorption (μg/cm^2)	Post-SDS Adsorption (μg/cm^2)
6A	PVDF	12% HEMA	1.9 [48]	25.9	19.5
6B	PVDF	9% HEMA	1.8 [46]	28.8	23.9
6C	PVDF	9% HEMA	1.7 [43]	22.4	19.6
6D	PVDF	4% HPA	1.7 [43]	12.4	8.8
6E	PVDF	none	1.6 [41]	-	86.6
6F	PVDF	none	1.5 [38]	-	82.6

25   The resulting data demonstrates that a filtration membrane of the present invention which has been suitably graft polymerized will have a low protein adsorption level. The present inventive membranes grafted with hydroxyethylmethacrylate (HEMA) exhibited a much reduced
30   level of protein adsorption as compared to the ungrafted controls. Moreover, the present inventive membrane grafted with hydroxypropylacrylate (HPA) adsorbed only about half as much protein as the HEMA-grafted membranes of the present invention.

Example 7

This example illustrates that the microwave drying
of the present inventive membrane has no significant
adverse effect on the filtration characteristics of the
5   membrane.

Two membrane samples were prepared in accordance
with the procedure described in Example 1. One of the
membranes was dried with a microwave dryer (designated
7A), while the other of the membranes was dried with a
10   steam drum-dryer (designated 7B). The K_{UF} values of the
two membranes were determined both before and after
drying, and the results are set forth below.

Sample	K_{UF} (as cast) (psi) [kPa]	K_{UF} (dried) (psi) [kPa]
7A	22 [152]	21 [145]
7B	22 [152]	17 [117]

These results demonstrate that microwave drying of
the membranes, in contrast to conventional drying, does
not substantially affect the pore size of the present
20   inventive membrane.

Example 8

This example illustrates the isotropic nature, i.e.,
symmetrical pore structure, of the present inventive
25   membrane.

Several membranes of differing K_{UF} values were
prepared in accordance with the procedure described in
Example 1. The K_{UF} and pressure drop (ΔP) divided by
thickness (in. Hg/mil and cm Hg/μm) for each membrane
30   were determined, and the results are set forth below.

33

	Sample	K_{UF} (psi) [kPa]	ΔP/mil (in. Hg/mil) [cm Hg/μm]
	8A	12 [83]	1.50 [0.15]
	8B	12 [83]	1.32 [0.13]
	8C	13 [90]	1.50 [0.15]
5	8D	16 [110]	3.27 [0.33]
	8E	17 [117]	2.84 [0.28]
	8F	17 [117]	2.93 [0.29]
	8G	17 [117]	2.63 [0.26]
	8H	17 [117]	4.27 [0.43]
10	8I	18 [124]	2.65 [0.27]
	8J	18 [124]	4.06 [0.41]
	8K	19 [131]	3.90 [0.39]
	8L	21 [145]	11.20 [1.12]
	8M	21 [145]	5.33 [0.53]
15	8N	22 [152]	20.75 [2.08]
	8O	22 [152]	7.85 [0.79]
	8P	23 [159]	8.00 [0.80]
	8Q	23 [159]	14.40 [1.44]
	8R	23 [159]	11.00 [1.10]
20	8S	24 [165]	12.08 [1.21]
	8T	24 [165]	14.96 [1.50]
	8U	24 [165]	14.07 [1.41]
	8V	24 [165]	11.93 [1.19]
	8W	24 [165]	14.52 [1.45]
25	8X	24 [165]	9.70 [0.97]
	8Y	25 [172]	22.27 [2.23]

The resulting data is plotted in the form of pressure drop across the membrane (ΔP) divided by the thickness of the membrane (in. Hg/mil and cm Hg/μm) on a logarithmic scale versus membrane K_{UF} (psi and kPa) as

5 the graph of Figure 4. The drawn curve is the result of a least squares fit and has a correlation factor of 0.87. As is apparent from the data, an increase in the K_{UF} results in a logarithmic increase in the pressure drop as a function of thickness of the filtration

10 membrane. This relationship is characteristic of an isotropic filtration membrane, and confirms that the present inventive filtration medium is isotropic in nature.

15 While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred products and methods may be used and that it is intended that the invention may be practiced

20 otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1.   An isotropic, skinless, porous, polyvinylidene fluoride membrane having a K_{UF} of at least 15 psi when tested using liquid pairs having an interfacial tension of about 4 dynes/cm.

2.   The membrane of claim 1, wherein said membrane has a K_{UF} of 15 psi to 50 psi.

3.   The membrane of claim 1 or 2, wherein said membrane has a K_{UF} of at least 17 psi.

4.   The membrane of claim 3, wherein said membrane has a K_{UF} of 17 psi to 40 psi.

5.   The membrane of claim 4, wherein said membrane has a K_{UF} of 18 psi to 30 psi.

6.   An isotropic, skinless, porous polyvinylidene fluoride membrane having a titer reduction of at least 10^8 against T_1 bacteriophage.

7.   The membrane of claim 6, wherein said membrane has a titer reduction of 10^2 or less against PP7 bacteriophage.

8.   The membrane of claim 6, wherein said membrane has a titer reduction of at least 10^8 against PR772 coliphage.

9.   The membrane of claim 8, wherein said membrane has a titer reduction of 10^2 or less against PP7 bacteriophage.

10.   The membrane of claim 8, wherein said membrane has a titer reduction of at least 10^8 against PP7 bacteriophage.

11.   The membrane of any one of claims 6 to 10, wherein said membrane has a thickness of 20 mil or less.

12.   The membrane of claim 11, wherein said membrane has a thickness of 5 mil or less.

13.   The membrane of claim 12, wherein said membrane has a thickness of 3 mil to 5 mil.

14.   The membrane of any one of claims 6 to 13, wherein said membrane has a K_{UF} of at least 15 psi when tested using liquid pairs having an interfacial tension of about 4 dynes/cm.

15.   The membrane of claim 14, wherein said membrane has a K_{UF} of 15 psi to 50 psi.

16.   The membrane of any one of claims 6 to 13, wherein said membrane has a K_{UF} of at least 17 psi.

17.   The membrane of claim 16, wherein said membrane has a K_{UF} of 17 psi to 40 psi.

18.   The membrane of claim 17, wherein said membrane has a K_{UF} of 18 psi to 30 psi.

19.   The membrane of any one of claims 1 to 18, wherein said membrane comprises a surface coating of a polymer rendering said membrane hydrophilic and less susceptible to the adsorption of proteins.

20.   The membrane of claim 19, wherein said polymer comprises one or more acrylic or methacrylic monomers having hydroxyl functional groups.

21. The membrane of claim 20, wherein said polymer comprises one or more monomers selected from the group consisting of hydroxyethylacrylate, hydroxyethyl-methacrylate, hydroxypropylacrylate, and hydroxypropyl-methacrylate.

22. The membrane of claim 21, wherein said polymer comprises hydroxyethylmethacrylate, hydroxypropylacrylate, or a combination thereof.

23. The membrane of claim 22, wherein said polymer comprises hydroxypropylacrylate.

24. The membrane of claim 22 or 23, wherein said polymer further comprises polyethylene glycol 600 dimethacrylate.

25. The membrane of any one of claims 20 to 24, wherein said polymer has been radiation grafted onto said membrane.

26. The membrane of claim 25, wherein said radiation is electron beam radiation.

27. A method of preparing a porous membrane wherein the improvement comprises drying a wet cast membrane by exposing said membrane to microwave radiation under conditions sufficient to effect the removal of liquid from said membrane.

28. The method of claim 27, wherein said membrane comprises polyvinylidene fluoride.

29. A method of preparing a membrane, comprising: providing a casting solution comprising polyvinylidene fluoride and a solvent therefor, heating said casting solution to a uniform temperature of 57°C to 60°C, spreading said casting solution onto a substrate to form a film, quenching said film in a quench bath so as to form a porous membrane, and washing and drying said porous membrane.

30. The method of claim 29, wherein said casting solution temperature is 58°C to 60°C.

31. The method of claim 29 or 30, wherein said membrane is at least partially dried by exposing said membrane to microwave radiation.

32. The method of claim 29, 30 or 31, wherein said membrane is treated to render said membrane hydrophilic and less susceptible to the adsorption of proteins.

33. The method of claim 32, wherein said treatment comprises bonding to the surface of said membrane a polymer comprising one or more acrylic or methacrylic monomers having hydroxyl functional groups.

34. The method of claim 33, wherein said polymer comprises one or more monomers selected from the group consisting of hydroxyethylacrylate, hydroxyethyl-methacrylate, hydroxypropylacrylate, and hydroxypropyl-methacrylate.

35. The method of claim 34, wherein said polymer comprises hydroxyethylmethacrylate, hydroxypropylacrylate, or a combination thereof.

36. The membrane of claim 35, wherein said polymer further comprises polyethylene glycol 600 dimethacrylate.

37. The membrane of claim 35, wherein said polymer comprises hydroxypropylacrylate.

38. The membrane of claim 37, wherein said polymer further comprises polyethylene glycol 600 dimethacrylate.

39. The method of any one of claims 33 to 38, wherein said polymer is radiation grafted onto said membrane.

40. The method of claim 39, wherein said radiation is electron beam radiation.

41. A membrane prepared in accordance with the method of any one of claims 29 to 40.

42. A method of filtering a fluid, which comprises passing the fluid through a membrane of any one of claims 1 to 26.

43. The method of claim 42, wherein the fluid comprises viruses in excess of 10^2/ml before being passed through said membrane, but less than 10^2/ml after being passed through said membrane.

44. The method of claim 43, wherein the fluid comprises viruses in excess of 10^4/ml before being passed through said membrane.

45. The method of claim 43 or 44, wherein the fluid comprises no viruses after being passed through said membrane.

46. The method of claim 42, wherein the fluid comprises viruses.

47. The method of claim 46, wherein the fluid comprises no viruses after being passed through said membrane.

48. A filter element comprising a membrane of any one of claims 1 to 26 having sides which have been overlapped and sealed to form a tubular configuration having an exterior surface, an interior and two ends, and end caps sealed to the ends of the tube, wherein at least one of said end caps has a central aperture providing access to the interior of the tube, and all of said seals are fluid-tight.

49. The filter element of claim 48, wherein said membrane is corrugated.

50. The filter element of claim 48 or 49, wherein at least one of the sides of said membrane is adhered to a porous support layer.

51. The filter element of claim 50, wherein said membrane and said porous support layer are corrugated.

52. The filter element of claim 51, wherein said filter element comprises multiple membranes adhered together.

53. The filter element of claim 52, wherein said membranes are separated by a porous support layer to which each membrane is adhered.

UNSCANNABLE ITEM   (Dwg)

RECEIVED WITH THIS APPLICATION

(ITEM ON THE 10TH FLOOR ZONE 5 IN THE FILE PREPARATION SECTION)

DOCUMENT REÇU AVEC CETTE DEMANDE

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(DOCUMENT AU 10 IÈME ÉTAGE AIRE 5 DANS LA SECTION DE LA
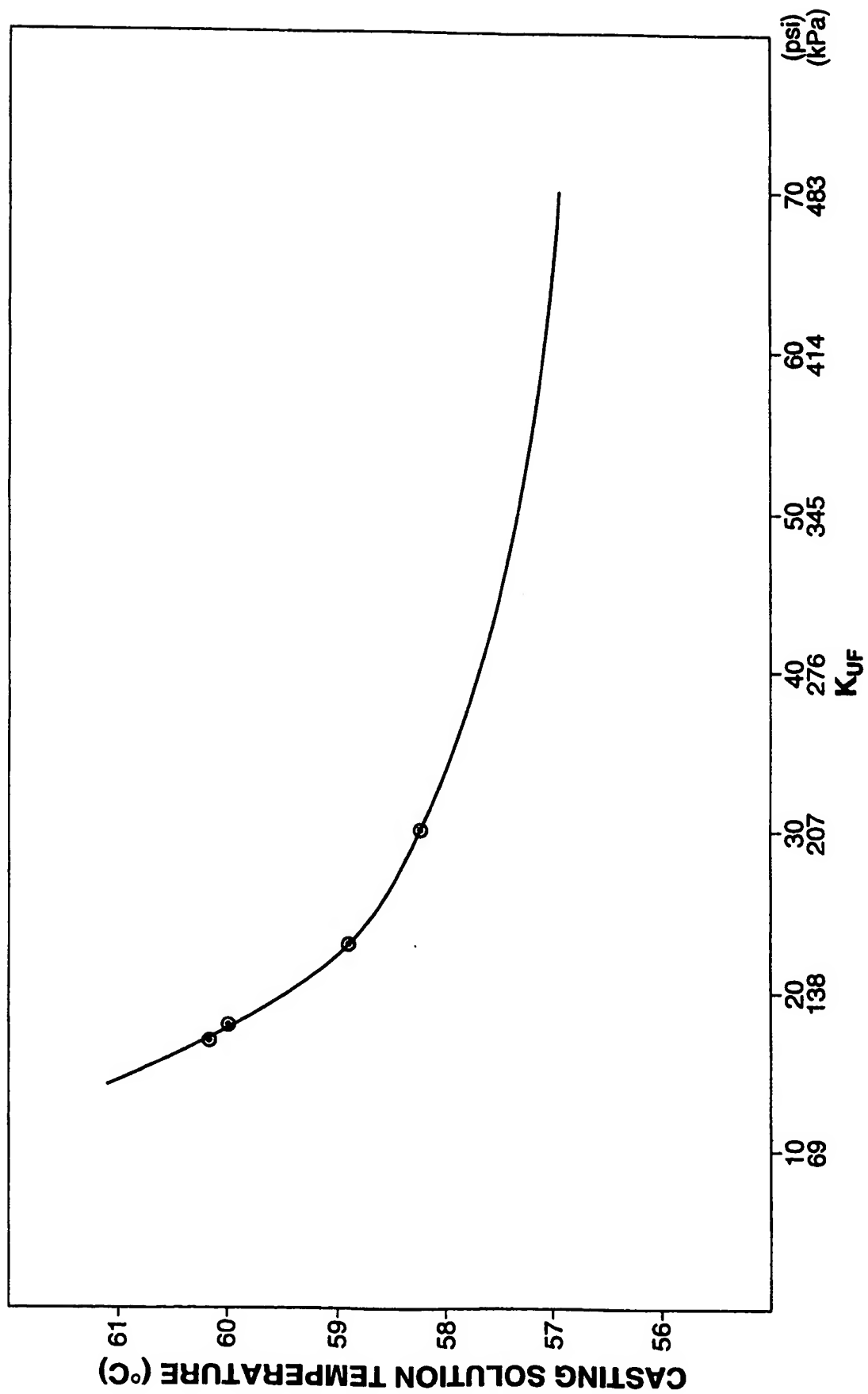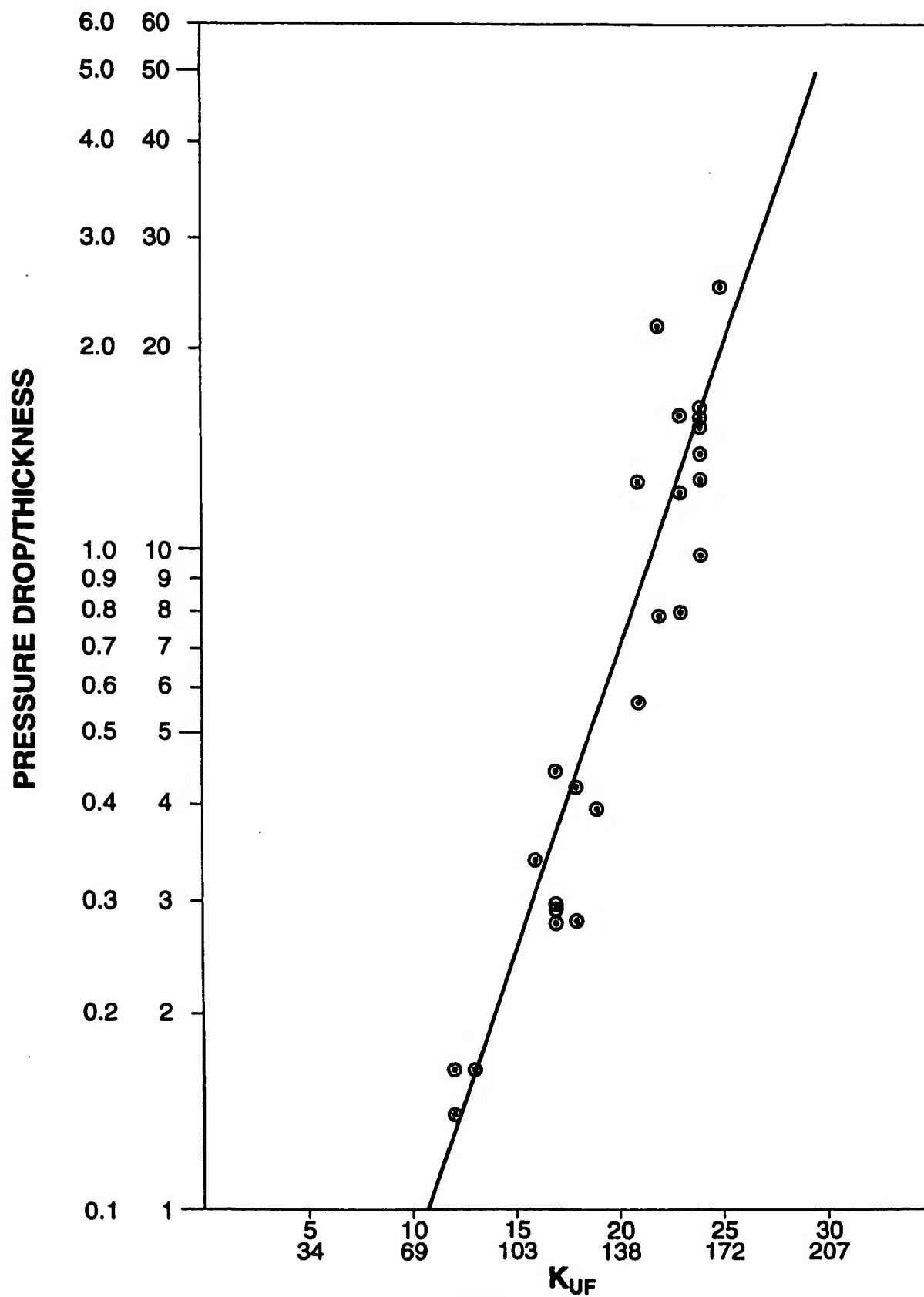
PRÉPARATION DES DOSSIERS)

FIG. 3

FIG. 4